PATENT
Docket No.: 1662/492021

IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

Reissue of U.S. 6,365,574 B2

In Re Reissue Application of:

Applicant:	Claude SINGER et al.
Serial No.	10/816,376
Filed:	April 2, 2004
Group Art Unit:	1623
Examiner:	E. Peselev
For:	ETHANOLATE OF AZITHROMYCIN, PROCESS FOR MANUFACTURE, AND PHARMACEUTICAL COMPOSITIONS THEREOF

Assistant Commissioner for Patents
PO Box 1450
Alexandria, VA 22313-1450

DECLARATION OF JUDITH ARONHIME PURSUANT TO 37 C.F.R. §1.132

I, JUDITH ARONHIME, Ph.D., of Harav Maor Yosef str. 5a, Rehovot 76217, Israel, declare as follows:

1. I am a named inventor of the above-identified reissue application ("the '376 reissue application"). The '376 reissue application seeks reissue of U.S. Patent No. 6,365,574 ("the '574 patent"), for which I am also a named inventor.

   Note: Because the '376 reissue application and the '574 patent share the same specification, reference will be made hereinafter to the '376 reissue application with the understanding that, where specified, column and/or line number refer to the '574 patent.

2. I received my Ph.D. and M.Sc. degrees in 1989 and 1983, respectively, from The Hebrew University of Jerusalem, Casali Inst. of Applied Chemistry. Since 1991, I have worked for Teva Pharmaceutical Industries, Ltd. ("Teva"). I am currently Teva's Global Solid State Characterization Manager. In that position, I am responsible for the physical analysis and characterization of drugs developed by Teva API ("Active Pharmaceutical Ingredients"). I am responsible for over 15 analysts in the group.

3. I am aware of the following pending U.S. Patent Applications, which I believe are assigned to Pfizer, Inc.:

(1) Ser. No. 10/650,252 ("the '252 application"), filed August 27, 2003;

(2) Ser. No. 10/650,253, ("the '253 application"), filed August 27, 2003; and,

(3) Ser. No. 10/652,655 ("the '655 application"), filed August 28, 2003.

Collectively, the '252, '253 and '655 applications are referred to herein as "the Pfizer applications."

4. I have read and understand the Pfizer applications. Each of these applications was filed as a continuation of a common parent application (ser. no. 10/152,106, filed May 21, 2002) and thus shares an identical specification.

Note: Because each of the Pfizer applications has an identical specification, reference will be made hereinafter to the '252 application with the understanding that, where specified, paragraph numbers refer to those in U.S. Patent Application Publication No. 2004/0043944 A1, which is the published version of the '252 application.

5. I have also read and understand the currently pending claims in each of the Pfizer applications. Each of these applications has only one independent claim directed to some aspect of "substantially pure form F azithromycin." The pending independent claims in each of these applications are as follows:

(1) the '252 application:

87. An azithromycin mixture comprising substantially pure form F azithromycin and optionally azithromycin dihydrate.

(2) the '253 application:

124. A pharmaceutical dosage form comprising said substantially pure Form F and a pharmaceutically acceptable carrier or diluent.

(3) the '655 application:

124. A crystalline form of azithromycin, wherein said form is substantially pure Form F.

6. The Pfizer applications characterize Form F in the following manner:

Par. [0007]:

Form F azithromycin is of the formula $C_{38}H_{72}N_2O_{12}.H_2O.0.5C_2H_5OH$ in the single crystal structure, being azithromycin monohydrate hemi-ethanol solvate. Form F is further characterized as containing 2-5% water and 1-4% ethanol by weight in powder samples and having powder X-ray diffraction 2θ peaks as defined in Table 9. The ^{13}C ssNMR (solid state Nuclear Magnetic Resonance) spectrum of form F has two chemical shift peaks at approximately 179±1 ppm, those being 179.5±0.2 ppm and 178.6±0.2 ppm, a set of five peaks between 6.4 to 11.0 ppm, and ethanol peaks at 58.0±0.5 ppm and 17.2±0.5 ppm. The solvent peaks can be broad and relatively weak in intensity.

At paragraph 85, the Pfizer applications further characterize Form F as follows:

Par. [0085]:

Form F: The single crystal of form F crystallized in a monoclinic space group, $P2_1$, with the asymmetric unit containing two azithromycin, two waters, and one ethanol, as a monohydrate/hemi-ethanolate (Table 5). It is isomorphic to all family I azithromycin crystalline forms. The calculated PXRD pattern of this form is similar to those of other family I isomorphs. The theoretical water and ethanol contents are 2.3 and 2.9%, respectively. The powder samples show a dehydration/desolvation endotherm at an onset temperature between 110-125° C. Form F is prepared by dissolving azithromycin in ethanol (1-3 volumes by weight) at a temperature of about 50-70° C. Upon complete dissolution, the solution is cooled to subambient

temperature to cause precipitation. The volume of ethanol can be reduced by vacuum distillation with stirring for 1-2 hours to increase the yield. Alternatively, water (optionally chilled to 0-20° C.) about 0.1-2 volume can be added with collection of solids within 30 minute after water addition. Cooling the ethanol solution of azithromycin prior to the addition of water to below below [sic] 20° C., preferably below 15° C., more preferably below 10, and most preferably 5° C. results in substantially pure azithromycin form F. The solid form F azithromycin is collected by filtration and dried.

In Table 5, the Pfizer applications provide the following data for Form F:

TABLE 5

Crystallographic data of azithromycin form F.

	Form F
Empirical formula	$C_{38}H_{72}N_2O_{12}.H_2O.0.5C_2H_5OH$
Crystal size (mm)	0.14 x 0.20 x 0.24
Formula weight	790.2
Space group	$P2_1$ monoclinic
Unit cell dimensions	a = 16.281 (2) Å
	b = 16.293 (1) Å
	c = 18.490 (3) Å
	α = 90°
	α= 109.33 (1)°
	γ = 90°
Z (per formula)	4
Density (g/cm.sup.3)	1.13
R	0.0688

7. The Pfizer applications define "substantially pure" in the following manner:

Par. [0033]:

> The term "substantially pure" when referring to a designated crystalline form of azithromycin means that the designated crystalline form contains less than 20% (by weight) of residual components such as alternate polymorphic or isomorphic crystalline form(s) of azithromycin. It is preferred that a substantially pure form of azithromycin contain less than 10% (by weight) of alternate polymorphic or isomorphic crystalline forms of azithromycin, more preferred is less than 5% (by weight) of alternate polymorphic or isomorphic crystalline forms of azithromycin, and most preferably less than 1% (by weight) of alternate polymorphic or isomorphic crystalline forms of azithromycin.

8. At par. [0006] the Pfizer applications state that Form F (and forms G, H, J, M, N, O and P) belong to "family I" azithromycin having a monoclinic $P2_1$ space group with cell dimensions a = 16.3±0.3 Å, b = 16.2±0.3 Å, and c = 18.4±0.3 Å and beta=109±2°. At par. [0006] the Pfizer applications state that forms C, D, E, and R belong to "family II" azithromycin having an orthorhombic $P2_12_12_1$ space group with cell dimensions a = 8.9±0.4 Å, b = 12.3±0.5 Å, and c = 45.8±0.3 Å. At par. [0006], the Pfizer applications define a "form Q" that is distinct from families I and II.

9. The Pfizer applications define "family I" and "family II" as "isomorphic families":

Par. [0079]

> Among these sixteen crystal forms, two isomorphic families are identified. Family I includes forms F, G, H, J, M, N, O, and P. Family II includes forms C, D, E and R. Form Q is distinct from families I and II. The forms within a family are isomorphs that crystallize in the same space group with slight variation of cell parameters and comprise chemically related structures but different elemental composition. In this case, the variation in chemical composition among the isomorphs arises from incorporation of different water/solvent molecules. Consequently, the isomorphs display similar but non-identical X-ray diffraction patterns and solid-state NMR spectra (ssNMR). Other techniques such as near infrared spectroscopy

(NIR), differential scanning calorimetry (DSC), gas chromatography (GC), thermalgravimetric analysis (TGA), or thermalgravimetric analysis/infrared spectroscopy analysis (TG-IR), Karl Fischer water analysis (KF) and molecular modeling/visualization provide data for affirmative identification of isomorphs. Dehydration/desolvation temperatures were determined by DSC with a heating rate of 5° C./min.

10. Par. [0070] defines other forms of azithromycin: "form A" is defined as a "dihydrate"; form B is defined as a "non-stoichiometric hydrate"; and, "form L" and "form K" are defined as "metastable lower hydrate forms of A detected at high temperature."

11. The Pfizer applications further characterize the other forms as follows:

Par. [0080] "form C" is a monohydrate of azithromycin that belongs to the family II isomorphs

Par. [0081] "form D" is a monohydrate/monocyclohexane solvate

Par. [0083] "form E" is a monohydrate/mono-THF solvate

Par. [0086] "form G" is a sesquihydrate

Par. [0088] "form H" is a monohydrate/hemipropylene glycol solvate

Par. [0090] "form J" is a monohydrate/hemi n-propanol solvate

Par. [0092] "form K" is a lower hydrate of form A and is a metastable high temperature form

Par. [0093] "form L" is only observed upon heating the dihydrate and is a lower hydrate of form A

Par. [0094] "form M" is a monohydrate/hemi-isopropanolate

Par. [0096] "form N" is isolated from water/ethanol/isopropanol slurry of form A and may contain various amounts of the crystallization solvents and water; at par. [0105], form N is further characterized as "a mixture of Family I isomorphs by solvent composition and solid-state NMR data."

Par. [0098] "form O" is a hemihydrate hemi-n-butanol solvate

Par. [0100] "form P" is a hemihydrate hemi-n-pentanol solvate

Par. [0102] "form Q" exhibits a "unique" powder X-ray diffraction pattern, is a hydrate hemi-THF solvate

Par. [0104] "form R" (bulk) has a theoretical water content of 2.1 weight % and a theoretical methyl tert-butyl ether content of 10.3 weight %

12. The '376 reissue application discloses and claims an azithromycin ethanolate that:

a. by single crystal x-ray diffraction analysis performed on material made in accordance with the Example at col. 3 in the '376 reissue application, is azithromycin monohydrate hemi-ethanolate solvate, monoclinic, space group $P2_1$; this is consistent with the single crystal characterization of Form F;

EXHIBIT 1, attached to this declaration, is a report of a single crystal analysis conducted on this material.

b. in a powder sample, has an ethanol content of about 1.5% to about 3.0% w/w; and a water content of about 2% to about 4% w/w; this is consistent with the ethanol (1-4%) and water (2-5%) contents of a powder sample of Form F;

c. has a characteristic experimental powder X-ray diffraction ("PXRD") pattern, as set forth in Fig. 2 of the '376 reissue application; this is consistent with both the experimental PXRD of Form F, as shown in Fig. 9 of the Pfizer applications, and with the characteristic PXRD peaks of Form F as reported in Table 9 of the Pfizer applications; and,

d. has a solid state ^{13}C NMR spectra that is consistent with the solid state ^{13}C NMR spectra of Form F as shown in Fig. 23 of the Pfizer applications.

EXHIBIT 2, attached to this declaration, is a solid state NMR spectrum of a sample of azithromycin monohydrate hemiethanolate that I understand was prepared in accordance with the disclosure at col. 2, lns. 38-67 of the

'376 reissue application and the Example at col. 3 thereof. More specifically, this sample was prepared as follows:

Ten g of azithromycin crude were introduced into a 0.25 liter three-necked flat flanged jacketed vessel equipped with a mechanical stirrer, a condenser and thermometer and containing 30 ml of absolute ethanol at 25° C. 1.8 ml of water at 25° C were added and the solution was heated at a constant temperature gradient so as to reach 50° C after 5 hours. Between 35° C and 50° C, additional water having a total volume of 11 ml were slowly added at regular time intervals. When 50° C was reached, the resulting suspension was maintained at this temperature for 1 hour during which an additional 50.2 ml of water were added. The suspension was then cooled from 50° C to 20° C over 1 hour. The precipitate was filtered and dried.

This sample is the material prepared by Experiment 3, referred to in paragraph 16, below, the parameters of which are reported in the col. "Exp 3" in the table attached hereto at EXHIBIT 3.

13. Based on the comparative analysis as set forth in paragraph 12, I conclude that the azithromycin ethanolate disclosed and claimed in the '376 reissue application is the same solid state form as azithromycin Form F as disclosed and claimed in the Pfizer applications.

14. I understand that, as set forth in paragraph 7, above, the Pfizer applications define "substantially pure Form F" as Form F containing "less than 20% (by weight) of residual components such as alternate polymorphic or isomorphic forms of azithromycin."

15. The azithromycin ethanolate disclosed and claimed in '376 reissue application is "substantially pure" as that term is defined in the Pfizer applications, as set forth in paragraph 7, above. More specifically, the PXRD of the ethanolate disclosed and claimed in the '376 reissue application, as exemplified in Fig. 2 therein, is consistent with a material that contains less than 1% of any other isomorphic or polymorphic form of azithromycin.

16. In preparation for filing this reissue application, several samples of azithromycin ethanolate were prepared in accordance with the disclosure at col. 2, lns. 38-67 of

the '376 reissue application and the Example at col. 3 thereof. The specific parameters of those experiments are set forth in the table attached as EXHIBIT 3. Each of the samples thus prepared was analyzed by X-ray powder diffraction for detectable amounts of azithromycin dihydrate, named "form A" in the Pfizer applications. Within a detection limit of 1%, there was no detectable amount of the dihydrate found in any of the prepared samples. I believe that this data also shows that the ethanolate disclosed and claimed in the '376 reissue application is "substantially pure" as that term is defined in the Pfizer applications, as set forth in paragraph 7, above. More specifically, I believe that this data supports my conclusion that the ethanolate disclosed and claimed in the '376 reissue application contains less than 1% of any other isomorphic or polymorphic form of azithromycin. Based on structural and/or chemical differences, the samples so prepared would not be expected to include any detectable amount of any other "family 1" or "family 2" isomorph or form Q.

The family I isomorphic forms other than F are forms G, H, J, M, N, O, and P. Forms H, J, M, N, O and P all contain solvent molecules other than ethanol (i.e., propylene glycol, n-propanol, isopropanol, isopropanol, n-butanol and n-pentanol, respectively). Because forms G, H, J, M, N, O and P are isomorphic with form F, the possible presence of these forms would be assessed by determining the residual presence of these other solvents in the azithromycin ethanolate made as disclosed and claimed in the '376 reissue application. Ethanol is the only solvent (other than water) used in the process disclosed and claimed in the '376 reissue application. Therefore, azithromycin ethanolate made in accordance with the method disclosed and claimed in the '376 reissue application would not be expected to contain any detectable amount of any of forms H, J, M, N, O or P.

Form G is defined in the Pfizer applications as a sesquihydrate. Par. [0086] states that "[t]he water content of powder samples of form G ranges from about 2.5 to about 6%..." and the "[t]otal residual organic solvent is less than 1% of the corresponding solvent used for crystallization, which is well below stoichiometric quantities of solvate." Example 3, the only example in the Pfizer applications that discloses a method of preparing form G, discloses that it is prepared by crystallization from a methanol/water mixture followed by air drying and further vacuum oven drying. It is unclear from the disclosure of the Pfizer applications whether form G necessarily contains detectable residual methanol. Ethanol is the

only solvent (other than water) used in the process disclosed and claimed in the '376 reissue application. Therefore, regardless of whether form G contains detectable residual methanol, azithromycin ethanolate made in accordance with the method disclosed and claimed in the '376 reissue application, because it is not made using methanol, would not be expected to contain any detectable amount of form G.

The family II isomorphs are forms C, D, E, and R. None of the characteristic PXRD peaks of the family II isomorphs are evident in the diffractograms of azithromycin ethanolate made in accordance with the method disclosed and claimed in the '376 reissue application, including Fig. 2 therein. Therefore, on this basis alone, I conclude that there is no detectable amount of any family II isomorph in azithromycin ethanolate made in accordance with the method disclosed and claimed in the '376 reissue application. Moreover, forms D, E, and R all contain solvent molecules other than ethanol (i.e., cyclohexane, THF and tert-butyl methyl ether, respectively). Ethanol is the only solvent (other than water) used in the process disclosed and claimed in the '376 reissue application. Therefore, azithromycin ethanolate made in accordance with the method disclosed and claimed in the '376 reissue application would not be expected to contain any detectable amount of any of forms D, E and R.

Form Q, which is distinct from the family I and family II isomorphs, contains THF. Ethanol is the only solvent (other than water) used in the process disclosed and claimed in the '376 reissue application. Therefore, azithromycin ethanolate made in accordance with the method disclosed and claimed in the '376 reissue application would not be expected to contain any detectable amount of form Q.

17. I hereby declare that all statements made herein of my own knowledge are true and that all statements made on information and believe are believed to be true; and further that these statements were made with the knowledge that willful false statements and the like so made are punishable by fine or imprisonment, or both, under Section 1001 of Title 18 of the United States Code, and that such willful false statements may jeopardize the validity of the application or any patent issuing thereon.

Dated: 9.8.05 Signed: _____

Judith Aronhime, Ph.D.